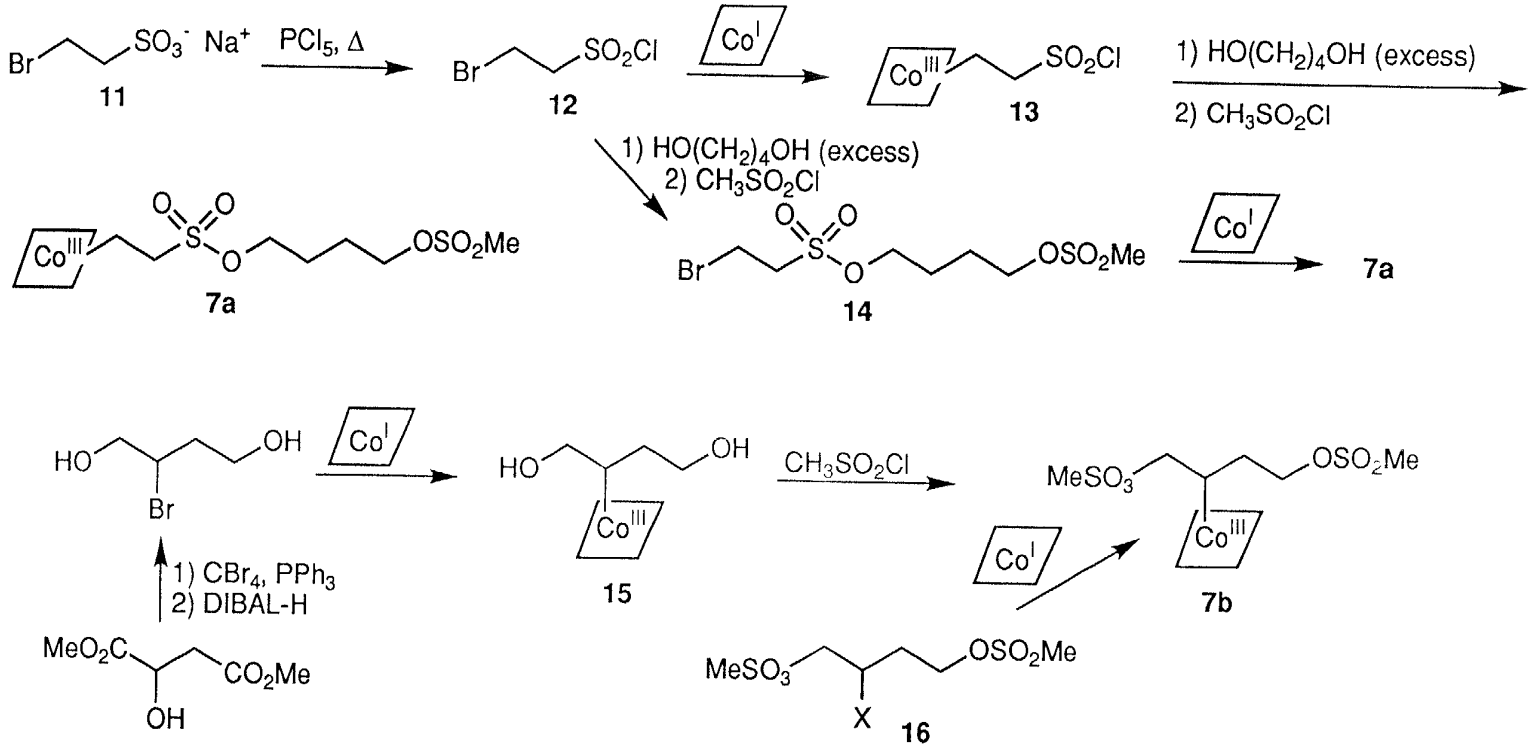

Br
SO3- Na+
PCl5, Δ
11
SO2Cl
12
Co(I)
Co(III)
13
1) HO(CH2)4OH (excess)
2) CH3SO2Cl
1) HO(CH2)4OH (excess)
2) CH3SO2Cl
OSO2Me
7a
14
7a
HO
OH
Br
1) CBr4, PPh3
2) DIBAL-H
MeO2C
CO2Me
OH
15
CH3SO2Cl
MeSO3
OSO2Me
7b
16
X

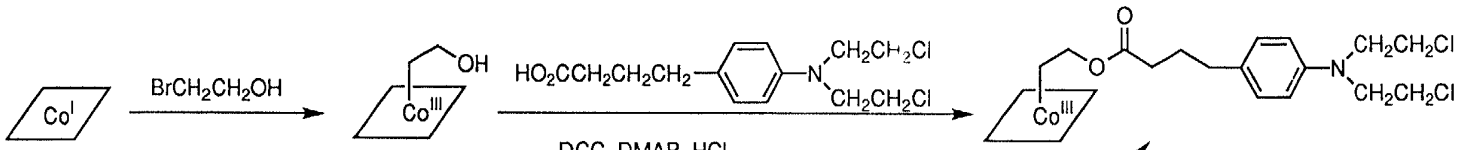
A chlorambucil-containing bioconjugate can be synthesized by the following methods. Chlorambucil is a relatively stable nitrogen mustard with attenuated alkylating ability, presumably as a consequence of the less-basic aniline nitrogen.

Method One: In this procedure, chlorambucil is converted to the acid chloride followed by reaction with cob(I)alamin or Co(I)[SALEN] according to reaction sequence I. In situations where the acyl linkage to the organocobalt complex is too labile towards serum nucleophiles, two alternate bioconjugation procedures can be utilized.

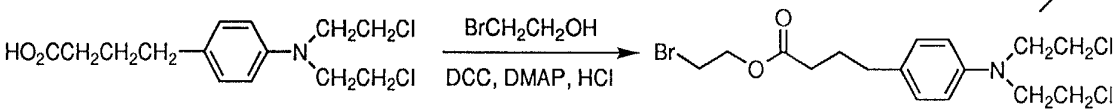
Method Two: The procedure involves bromination of a carbon atom adjacent to the carboxyl group under standard Hell-Vollhardt-Zelinski conditions to permit attachment of the Co complex in the α-position according to reaction sequence II. In scheme II, replacement of the C-Co with C-H provides chlorambucil. The reactant stoichiometry, temperature, and dilutions conditions can be manipulated to avoid competing displacement of one of the chloroethyl groups, or of the C1 by S_N2 attack.

Method Three: The BOC-protected p-aminophenylacetaldehyde can be conjugated to the Co moiety, followed by formation of the active nitrogen mustard product according to the following reaction sequence III.

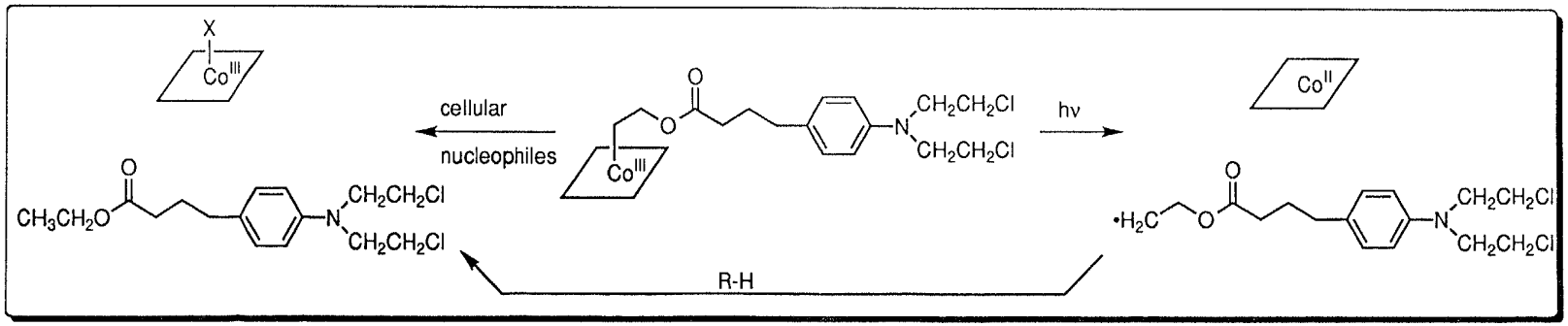
I


Co^{I}
BrCH$_2$CH$_2$OH
Co^{III}
OH
HO$_2$CCH$_2$CH$_2$CH$_2$
N
CH$_2$CH$_2$Cl
CH$_2$CH$_2$Cl
DCC, DMAP, HCl
O
Co^{III}

II


HO$_2$CCH$_2$CH$_2$CH$_2$
N
CH$_2$CH$_2$Cl
CH$_2$CH$_2$Cl
BrCH$_2$CH$_2$OH
DCC, DMAP, HCl
Br
O
Co^{I}

III


X
Co^{III}
cellular
nucleophiles
Co^{III}
hν
Co^{II}
CH$_3$CH$_2$O
•H$_2$C
N
CH$_2$CH$_2$Cl
CH$_2$CH$_2$Cl
R-H